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Epidemiology and Prevention: Workshop Report

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INTRODUCTION

THIS report is based on the contributions of the participants of this workshop who not only displayed posters but also gave oral presentations. The sections are, therefore, determined by the contents of proffered papers.

ANAMNESTIC FACTORS INFLUENCING BREAST CANCER RISK AND PROGNOSIS

There were two papers by Professor van Zyl and his colleagues, in the first of which Muller *et al.* [1] described the clinical and epidemiological profile of patients diagnosed as having breast cancer in the Cape, S. Africa in 1986. Of 159 patients, 76, 75 and eight were white, coloured and black, respectively. Coloured compared to white patients presented at a more advanced stage of the disease and older patients (> 50 years) in both groups presented at a more advanced stage of the disease although again the coloured patients had a worse prognosis. The few black women in this study presented at a more advanced stage of breast cancer. Coloured patients tended to be younger, have more nodes involved and have lower levels of oestrogen receptor [2]. These authors conclude that there could be an inherent biological difference in breast cancer of these two groups, although the possibility that the difference could be due to socio-economic status could not be eliminated. It was also pointed out that the Caucasians may be misrepresented since a proportion of them would have been treated privately.

The detailed pregnancy history of nearly all incident breast cancer cases (n = 1694) in Denmark over a 1 year period was accumulated [3]. Ever-pregnant women were significantly protected against risk of breast cancer the protective effect being positively related to the number of pregnancies. Women with at least one full-term pregnancy had 1/3 of the risk as women who had only an abortion in the first trimester. Contrary to dogma Dr. Ewertz reported that overall breast cancer risk was not related to age at first pregnancy even when standardized for multiparity. In discussion it was pointed out that the protective effect of early age at first full-term birth was not found in all studies. It was agreed that the differences could not be attributed to bad experimental design. Pike suggested that all the results were correct but that all confounding factors may not have been identified.

Leinster *et al.* [4] reported that high-risk mammographic patterns (Wolfe grade P2 + DY) in pre- and post-menopausal women were correlated with a variety of variables including previous benign breast disease, age at first pregnancy or body build. Therefore, if Wolfe grades are to be used as a method of screening women at high risk then these other factors should be considered.

There were three reports on the relationship between familial history of breast cancer and risk [5–7]. Wobbes *et al.* [5] reported that 14% of Dutch breast cancer patients had one, or more, first degree family members with the disease whilst Weber *et al.* [6] quoted 7% with two, or more, first or second degree affected relatives for Swiss breast cancer patients. Nomizu *et al.* [7] in their Japanese study on 39 families and Weber *et al.* [6] reported that women with a family history were younger at disease onset; they were about 10 years earlier compared with women without such a family history. The risk of bilateral disease was increased in women with a positive family history [6, 7]. In the Japanese study bilateral disease occurred in 33% of patients with a family history compared with only 0.9% of controls [7]. The opinion was made in discussion that a family history of breast cancer would be of little value in identifying high-risk groups for screening since these women would tend to have their disease earlier at an age when screening would be the least effective. It was also pointed out that in a normal population only about 10% would have a family history.

Ioannidou-Mouzaka *et al.* [9] using morphological criteria categorized breast tumours as being fatty (i.e. Wolfe's N1 pattern), intermediate or solid type and reported that the fatty type had a worse prognosis compared with patients of the solid type.

HORMONAL ASPECTS

(a) *Risk*

Den Tonkelaar *et al.* [8] studied the role of luteal phase dysfunction as a factor in breast cancer risk. In a prospective study involving 12,000 ostensibly normal women aged 40–49, 68 women were subsequently diagnosed as having breast cancer. After discarding 15 of these cases for a variety of reasons the remainder showed no luteal phase abnormality based on the urinary excretion of pregnanediol. This is yet another result which casts doubt on luteal phase insufficiency as being an important determinant in breast cancer risk (see [10]). A possible confounding factor could be that women who subsequently develop breast cancer have a later age at menopause. However, whether age at menopause is a risk factor in premenopausal breast cancer was discussed.

Interest in the possible involvement of biologically available oestrogen was highlighted by the paper of McCaffrey *et al.* [11]. These workers reported a significant increase in the percentage of 'free' or non-protein-bound oestradiol in Australian breast cancer patients who were either postmenopausal or who had undergone hysterectomy. They reported a similar finding for women in Hong Kong. In a survey of the world literature Key showed that all studies had reported an increased percentage or amount of available oestradiol in patients with breast cancer compared with controls.

One difficulty associated with determining oral contraceptive (OC) use and breast cancer risk are the inaccuracies of self-reported OC-taking history. Van Leeuwen *et al.* [12] have tackled this problem by comparing self-reporting with prescribers records. They concluded that agreement was best for the first OC used or for the longest used OC, and that the quality of data for self-reported total duration of OC use was sufficiently good to evaluate duration–response relationships.

The topic of prolactin was discussed by Wang *et al.* [13] who performed multivariate analysis of blood prolactin levels and breast cancer risk factors on two population-based cohorts of normal premenopausal women living on the Island of Guernsey. There were approximately 2000 women in each group. Standardizing for, amongst other things, menstrual cycle status, time of day of blood sampling and body weight, it was found that there was a significant inverse relationship between blood prolactin levels and parity. This implies that the protective effect of multiparity could be mediated by a reduction in the amount of circulating blood prolactin. It also means that the sooner a woman commences having children the younger she will be in achieving a reduction in blood prolactin and that the protective effect of early age at first baby could be mediated through such a lowering of blood prolactin concentration.

(b) *Prevention*

This section of the workshop was initiated by the interesting suggestion of Costa *et al.* [14] that the synthetic retinoid *N*-4-hydroxyphenylretinamide (HPR) could be used as an agent for preventing breast cancer. This compound has been claimed to be less toxic than other known retinoids. This was confirmed in a limited trial of 100 patients randomized to placebo, 100, 200 or 300 mg HPR/day. The major side-effect was impaired night vision. This group intend to evaluate HPR by determining how effective it is in preventing contralateral breast cancer in a randomized clinical trial of 3400 patients.

Another suggestion for preventing breast cancer has been the use of tamoxifen [15]. However, the use of this agent could be associated with unacceptable side-effects and there were two contributions which dealt with this specific problem. Bruning *et al.* [16] examined the blood chemistry of postmenopausal women with early or advanced breast cancer and who were being treated with tamoxifen. They concluded that prolonged administration of tamoxifen would not be anticipated to be associated with an increase in cardio-vascular disorders. Janicke and Lochmuller [17] studied the blood endocrinology of post-menopausal women. They found increases in the amount of sex-hormone-binding globulin (SHBG), cortisol and thyroxine and a suppression in FSH, LH and prolactin and concluded that since they found the ratio of oestradiol to SHBG declined with treatment, they therefore argued that this did not seem to impair its anti-tumour activity.

The benefits of tamoxifen in treating women with breast cancer are now well established. This benefit and its minimal side-effects has led to the suggestions that tamoxifen could be used prophylactically against breast cancer or for the long-term treatment of benign breast disease. Such suggestions have resulted in ICI extending its toxicity testing and Dr. J.S. Patterson, ICI Pharmaceuticals, reported on the preliminary data from these tests. Using five different mutagenesis tests, tamoxifen was found not to be genotoxic. However, in rats fed 5, 20 or 35 mg/kg/day they have found that in the highest dose-treated rats five out of 100 to date have developed hepatocellular carcinomas. These occurred 31–37 weeks after commencing treatment. There was also evidence of increased cataract forma-

tion in high and mid dose groups. This long-term experiment is still in progress. Dr. Patterson stated that in ICI's opinion tamoxifen was inappropriate for the long-term treatment of women in non-malignant situations. In women with confirmed breast cancer, he reminded us that there was 1.5 million patient years of experience with tamoxifen during which no hepatic tumours had been reported to the Company, and continued usage in proven malignancy therefore appears fully justified.

NUTRITIONAL ASPECTS OF BREAST CANCER RISK AND PROGNOSIS

Pawlega [18] found that in Polish women a higher incidence of breast cancer was associated with urbanization, high income and an increased consumption of animal protein and alcohol. The quantity of fibre in the diet or obesity was not associated with breast cancer risk. Questioned about alcohol intake of Polish women, Dr. Pawlega commented that over recent years breast cancer incidence had increased in Poland as had alcohol consumption.

It has been pointed out by Bruning *et al.* [19] that the accumulation of fat in the gluteal–femoral region is related to female steroid activity whilst abdominal fat accumulation is associated with Western-life style. Thus, if diet is of importance in the risk of breast cancer, then this might be mediated by changes in, not only body weight, but also body shape. These workers have argued that increases in abdominal fat would be associated with increases in serum free fatty acids, which in turn would affect the amounts of biologically available oestradiol (see [11]). These workers have, therefore, started a prospective study to examine the relationship between body fat distribution and risk of subsequent breast cancer.

R.D. Bulbrook listed the possible strategies available for preventing breast cancer and discussed the efficacy, practicality and ethics of these measures and the methods available for identifying high risk groups of women.

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